REMARKS

Claims 1-7 were originally pending in the application. Claims 1-7 were rejected. No claims were allowed.

Claims 1 and 7 have been presently cancelled without prejudice or disclaimer. Claims 2-6 have been amended to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Specifically, claims 2-5 have been amended to delete reference to the term "novel" in their preambles and to remove their dependency from claim 1. Claim 2 is now an independent claim, from which claims 3-5 depend. Claims 2, 3 and 5 have also been amended to specifically incorporate by reference Figs. 1, 2 and 4, respectively, rather than specific peaks and bands. Support for these amendments can be found throughout the specification and claims as originally filed, *e.g.*, page 6, lines 3-4; page 8, line 2; page 8, lines 16-17.

Claim 6 has been amended to correct several minor grammatical errors and to delete reference to the term "novel" in the preamble, the phrase "(which is prepared according to example 3 of our earlier patent application having the reg No. 555/MAS/02 which is under process at IPO office India)" in step (a), and preferred embodiments throughout the claim. Claim 6 has also been amended to depend from claim 2.

New claims 8-12 are being added, dependent from claim 2. These claims are based on the description and original claims.

No new matter has been introduced by these amendments.

Reconsideration of the claim rejections and allowance of the pending claims in view of the amendments above and following remarks are respectfully requested.

Claim Rejections – 35 U.S.C. § 112

(a) Claims 1-5 or 7 were rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. According to the Examiner, it is unclear what "novel crystalline form VI" or crystalline form VI with IR, fig. 3, etc." means. Claims 1 and 7 have now been canceled, thereby rendering moot the rejection with respect to these claims. With respect to claims 2-6, Applicants respectfully traverse the basis for rejection.

Claims 2-6 have been amended to delete reference to the term "novel" and to remove their dependency from claim 1. Claim 2 is now an independent claim, from which claims 3-5 depend. Applicants submit that the 1-benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]methyl-piperidine hydrochloride (donepezil hydrochloride) of claims 2-6 is clearly defined in terms of its X-ray powder diffraction pattern, IR absorption spectrum, TGA thermogram and DSC thermogram. Accordingly, Applicants submit that claims 2-6 are not indefinite, and reconsideration of this basis for rejection is respectfully requested.

(b) Claim 7 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. According to the Examiner, Claim 7 includes multiple categories of invention, *i.e.*, a product and a process. Claim 7 has been cancelled, thereby rendering moot the rejection.

(c) Claim 6 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. According to the Examiner, the critical starting material for the claim (donepezil free base) was defined with reference to an Indian patent application, which is not available to the public. Applicants respectfully traverse this basis for rejection.

Claim 6 has been amended to delete reference to "reg No. 555/MAS/02" in step (a). However, the preparation of donepezil free base is clearly described in numerous patent and other publications available to the skilled artisan as of the priority date of the instant application, including U.S. Patent No. 4,895,841 (of record), U.S. Patent Nos. 5,606,065 and 6,252,081, and International Application Publication No. WO 97/22584 (discussed in reg No. 555/MAS/02 itself). Accordingly, Applicants submit that claim 6 is enabled, and reconsideration of this basis for rejection is respectfully requested.

Claim Rejections – 35 U.S.C. § 102

(a) Claim 1 was rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Sugimoto et al. (U.S. Patent No. 4,895,841; "Sugimoto"). According to the Examiner, Sugimoto discloses donepezil hydrochloride at col. 34, Example 4. Claim 1 has been cancelled, thereby rendering moot the rejection.

(b) Claims 5 and 6 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Imai et al. (U.S. Patent No. 5,985,864; "Imai"). According to the Examiner, Imai discloses at column 7, line 13 crystalline donepezil hydrochloride with a melting point of 229° C and a process for its preparation at column 8, lines 20-24 or column 15, example 18. Applicants respectfully traverse this basis for rejection.

According to MPEP § 2131:

> A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently descried, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 638, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Contrary to the Examiner's position, Imai does not disclose crystalline donepezil hydrochloride, nor a process for its preparation, having each and every limitation as set forth in claims 5 and 6 of the instant application.

Claim 5 now depends from claim 2 and is thus directed to crystalline donepezil HCl form VI having an X-ray powder diffraction pattern substantially as depicted in Fig. 1. Imai, on the other hand, discloses at column 7, line 13 crystalline donepezil hydrochloride form III. The X-ray powder diffraction pattern of crystalline donepezil hydrochloride form III, shown in Fig. 3 of Imai, is substantially different from that of crystalline donepezil hydrochloride form VI depicted in Fig. 1 of the instant application. Indeed, the absence of an anticipation rejection for claim 2 indicates that the Examiner recognizes the difference in X-ray powder diffraction patterns. In addition, as the Examiner notes, crystalline donepezil hydrochloride form III of Imai has a melting point of 229-231° C, whereas the melting point of the instant crystalline donepezil hydrochloride form VI is 222-225° C (*see* page 8, lines 3-4). Accordingly, Applicants submit that claim 5 is not anticipated by Imai, and reconsideration of this basis for rejection is respectfully requested.

Claim 6 also now depends from claim 2 and thus is directed to a process for preparing crystalline donepezil hydrochloride form VI having an X-ray powder diffraction pattern substantially as depicted in Fig. 1. The passages in Imai cited by the Examiner, on the other hand, are directed to processes for the preparation of crystalline donepezil hydrochloride form III. As discussed above with respect to claim 5, crystalline donepezil

hydrochloride form III of Imai has a X-ray powder diffraction pattern substantially different from that of the instant crystalline donepezil hydrochloride form VI. Accordingly, Applicants submit that claim 6 is not anticipated by Imai, and reconsideration of this basis for rejection is respectfully requested.

Claim Rejection – 35 U.S.C. § 103

(a) Claims 1-7 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Sugimoto in view of Imai, and further in view of Doelker, *Ann. Pharm. Fr.* 60:161-176 (2002) ("Doelker"), Wikipedia, Article on Polymorphism, 1-2 (2006) ("Wikipedia"), Davidovich et al., *Am. Pharm. Rev.* 7:10, 12, 14, 16, 100 (2004) ("Davidovich"), or U.S Pharmacopeia #23 (1995) ("USP #23").

According to the Examiner, Sugimoto discloses anticipatory compounds of donepezil hydrochloride, while Imai discloses that this compound exhibits polymorphism, and further discloses that at least one polymorphic crystalline form has the same melting point, as well as an anticipatory process for making the polymorph. Doelker, Wikipedia and Davidovich, according to the Examiner, disclose that most pharmaceutical compounds have different polymorphic forms, that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound, and that differences in X-ray diffraction patterns may or may not be indicative of true polymorphism. Thus, according to the Examiner, one having ordinary skill in the art in possession of these references would find the instant claims *prima facie* obvious because the prior art discloses the same pure compound and its multiple crystalline forms, with at least one polymorphic crystalline form having the same melting point. It is well recognized in the art, according to the Examiner, that X-ray diffraction patterns may have different appearances due to artifacts and choice of solvent, and must be carefully evaluated for true polymorphism. Further, according to the Examiner, Imai discloses an identical process of making the claimed compound, and the picking and choosing among the variations of operation in crystallization among the choices disclosed in Imai to obtain variations in crystalline properties with innately minor differences in X-ray diffraction patterns would be prima

facie obvious since such is the expected results conventionally known to one having ordinary skill in the art.

Claims 1 and 7 have been canceled, thereby rendering moot the rejection with respect to these claims. With respect to claims 2-6, Applicants respectfully traverse this basis for rejection.

According to MPEP § 706.02(j):

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Thus, to sustain the rejection of obviousness, the cited references must provide all the limitations of claims 2-6. However, the cited references, alone or in combination, fail to teach or suggest all such claim limitations, in particular the existence of crystalline donepezil hydrochloride form VI having X-ray powder diffraction pattern substantially depicted as in Fig. 1.

With regard to Sugimoto, although the reference discloses the preparation of donepezil hydrochloride in Example 4, there is no teaching or suggestion that donepezil hydrochloride exists in different polymorphic forms, let alone the crystalline donepezil hydrochloride form VI recited in claims 2-6 of the instant application. In addition, the melting point given for donepezil hydrochloride in Example 4 of Sugimoto is 211-212° C, significantly different from the 222-225° C melting point of the instant crystalline donepezil hydrochloride form VI.

With regard to Imai, as discussed above with respect to the second § 102(b) rejection, the portions cited by the Examiner teach the preparation of crystalline donepezil hydrochloride form III, whose X-ray powder diffraction pattern shown in Fig. 3 in Imai is substantially different from that shown for the instant crystalline donepezil hydrochloride form VI in Fig. 1 of the instant application. As is the case with Sugimoto,

there is no teaching or suggestion in Imai that donepezil hydrochloride exists as the form VI recited in claims 2-6 of the instant application. Furthermore, the Examiner is mistaken that crystalline donepezil hydrochloride form III of Imai has the same melting point as the instant crystalline donepezil hydrochloride form VI. As discussed above, form III has a melting point of 229-231° C, whereas the melting point of the instant form VI is 222-225° C.

With regard to Doelker, Wikipedia, Davidovich and USP #23 (of which Wikipedia and Davidovich are not even prior art to the instant application), these ancillary references merely provide general background information relating to the study and preparation of polymorphs or case histories of specific polymorphic compounds (none of which is donepezil hydrochloride), and thus add nothing over the primary references.

Applicants object to the use of a Wikipedia article in the rejection. Since, the article can be anonymously modified at any time by anyone having Internet access, regardless of the individual's technical expertise, such articles are not reliable indicators of the knowledge possessed by a person having ordinary skill in the art.

With regard to the Examiner's position that Davidovich and USP teach, *inter alia*, that X-ray powder diffraction patterns may have different appearances due to artifacts and choice of solvent, rather than true polymorphism, Applicants submit that the large differences between the X-ray powder diffraction patterns for crystalline donepezil hydrochloride form III of Imai and the instant crystalline donepezil hydrochloride form VI are simply not the type of minor variation contemplated by Davidovich and USP #23 as being due to artifacts rather than true polymorphism. *See* Davidovich, at 12 (referring to such changes as "small") and USP #23, at 1843 (referring to such changes as "relatively minor").

Even a cursory comparison of Fig. 3 of Imai with Fig. 1 of the instant application reveals that the X-ray diffraction pattern for the instant crystalline donepezil hydrochloride form VI is significantly different from that for crystalline donepezil hydrochloride form III of Imai. For example, the instant form VI exhibits peaks at the low end of the 2-theta scale at about 14.22, 14.40 and 14.65 degrees 2-theta which are not present in the X-ray diffraction pattern for form III of Imai, while form III of Imai exhibits peaks at the low end of the 2-theta scale at about 6.56, 13.00 and 15.00 degrees 2-

theta not present in the X-ray diffraction pattern for the instant form VI, even given the usual margins of error associated with X-ray powder diffraction analyses. That the instant crystalline donepezil hydrochloride form VI and the crystalline donepezil hydrochloride form III of Imai are indeed distinct polymorphs is again supported by the difference in their respective melting points: 229-231° C for the instant form VI and 222-225° C for form III of Imai.

This failure of the cited references to teach or suggest the existence of crystalline donepezil hydrochloride form VI having X-ray powder diffraction pattern substantially depicted as in Fig. 1 is enough to overcome the Examiner's obviousness rejection. *See Ex parte Havens*, Appeal No. 2001-0091 for Application No. 08/732,254 (now U.S. Patent 6,452,007 B1) (BPAI 2001) ("The examiner's obviousness rejection seems to suffer the same infirmity as her anticipation rejection . . . The examiner has provided no evidence or convincing reason why the prior art disclosure of delavirdine mesylate in an undefined state would have suggested the specific S and T crystal forms that are the subject of the instant claims.") (emphasis added).

In addition, contrary to the Examiner's position, the proper test for obviousness in this case is not whether the existence of donepezil hydrochloride polymorphs is suggested by the prior art, but whether it would have been obvious to make the particular donepezil hydrochloride form VI disclosed and claimed in the instant application based on the prior art:

> The law of § 103 requires quite a different inquiry from that conducted by the ALJ. The correct inquiry is not whether the Bouzard monohydrate [polymorph] could have been produced by manipulation of other cefadroxil processes, once the existence of the Bouzard monohydrate was known. The question is whether it would have been obvious to make the Bouzard monohydrate, based on the prior art.

Bristol-Myers Co. v. U.S. Int'l Trade Comm'n, 892 F.2d 1050, (Fed. Cir. 1989) (unpublished decision) (emphasis added).

The matter of polymorphism in the pharmaceutical industry is not trivial. Accompanying this response is a copy of an eight-page website reprint of the article by A. Goho, "Tricky Business," *Science News*, Vol. 166, pages 122-3, August 21, 2004. This article discusses the importance of polymorphic form to drug performance, and

clearly describes the unpredictablility of the existence of yet-unidentified polymorphic forms and the processes that might be used to produce them. Since none of the cited documents disclose or predict the existence of the claimed donepezil hydrochloride form VI, it cannot possibly be considered obvious.

Here, the references cited by the Examiner suggest at most the mere possibility of finding additional donepezil hydrochloride polymorphs. Again, the Examiner has pointed to nothing in the cited references, either alone or in combination, which would suggest to one skilled in the art the particular donepezil hydrochloride form VI disclosed and claimed in the instant application, or a method for its preparation. Accordingly, Applicants submit that claims 2-6 are not rendered *prima facie* obvious under § 103(a) by Sugimoto in view of Imai in further view of Doelker, Wikipedia, Davidovich or USP #23, and reconsideration of this basis for rejection is respectfully requested.

It is believed that claims 2-6 and 8-12 are in condition for allowance, and an early notice of their allowability is respectfully solicited. If any minor issues remain to be resolved, please contact the undersigned to arrange for a telephonic or personal interview, so that a prompt resolution can be obtained.

Respectfully submitted,

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